NASA TECHNICAL MEMORANDUM

NASA TM-76044

FEATURES OF CHOLINERGIC CARDIA REGULATION UNDER CONDITIONS OF HYPOKINESIA

Ye. A. Markova, Yu. I. Bondarenko, V. A. Bolyarskaya, V. V. Fayfura, A. P. Rosolovskiy, and L. N. Babinskaya

Translation of "Osobennosti kholinergicheskoy regulyatsii serdtsa v usloviyakh gipokinezii", Patologicheskaya fiziologiya i eksperimental'naya terapiya, No. 3 (May-June), 1979, pp 13-16

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546 FEBRUARY 1980

STANDARD TITLE PAGE

1. Report No. NASA TM-76044	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle: Features of Cholinergic Cardiac Regulation Under Conditions of Hypokinesia		5. Report Date: February 1980 6. Performing Organization Code
7. Author(s): Ye. A. Markova, Yu. I. Bondarenko, V. A. Bolyarskaya, V. V. Fayfura, A. P. Rosolovskiy, and L. N. Babinskaya		8. Performing Organization Report No. 10. Work Unit No. 11. Contract or Grant No. NASw-3198
9. Performing Organization Name and Address: SCITRAN, Box 5456, Santa Barbara, CA 93108		13. Type of Report and Period Covered: Translation
12. Sponsoring Agency Name and Address: National Aeronautics and Space Administration, Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "Osobennosti kholinergicheskoy regulyatsii serdtsa v usloviyakh gipokinezii", Patologicheskaya fiziologiya i eksperimental'naya terapiya, No. 3 (May-June), 1979, pp 13-16

16. Abstract

The features of cholinergic processes in the heart on the 4th, 8th, 16th and 30th days of hypokinesia were studied in experiments on 382 albino rats. It was shown that hypokinesia is attended by increased acetylcholine content in the atria, reduced choline acetyltransferase activity in the atria and ventricles and by increased activity of acetylcholinesterase in the ventricles and of pseudocholinesterase in both parts of the heart. The sensitivity of the heart to exogenic acetylcholine and to stimulation of the vagus nerve increases.

17. Key Words (Selected by Author(s))	18. Distribution Statement	
	This copyrighted Soviet work is reproduced and sold by NTIS under license from VAAP, the Soviet copyright agency. No further copying is permitted without permission from VAAP.	
19. Security Classif. (of this report): Unclassified	20. Security Classif. (of this page): Unclassified	21. No. of Pages: 10
		22. Price

UDC 612.178.1-06:612.766.2

FEATURES OF CHOLINERGIC CARDIAC REGULATION UNDER CONDITIONS OF HYPOKINESIA

By Ye. A. Markova, Yu. I. Bondarenko, V. A. Bolyarskaya, V. V. Fayfura, A. P. Rosolovskiy, and L. N. Babinskaya, Department of Pathological Physiology of the Ternopol' Medical Institute

The features of cholinergic processes in the heart on the 4th, 8th, 16th and 30ieth days of hypokinesia were studied in experiments on 382 albino rats. It was shown that hypokinesia is attended by increased acetylcholine content in the atria, reduced choline acetyltransferase activity in the atria and ventricles and by increased activity of acetylcholinesterase in the ventricles and of pseudocholinesterase in both parts of the heart. The sensitivity of the heart to exogenic acetylcholine and to stimulation of the vagus nerve increases.

Clinical-physiological and experimental studies have demonstrated that /13* in the state of hypokinesia there is a lack of coordination in the coordinated activity of the regulatory systems in the organism. The functional state of the higher autonomous centers of the brain is sharply disrupted [9], the equilibrium between the parasympathetic and sympathetic sections of the autonomous nervous system is shifted [7], the activity of a number of organisms

*Numbers in margin indicate pagination in original foreign text

including the heart [6]. The importance of considering the cholinergic-adrenergic correlations in hypokinesia has found practical reflection in the recommendations to determine the biologically active substances under conditions of the effect of space flight factors [3] and the Kerde vegetative index to evaluate the state of the operators [4].

This work presents data on the features of cholinergic processes in the heart of rats during 30-day hypokinesia. There are very few articles on this question [1, 2, 5, 8].

Technique

Experiments were set up on 382 albino rats of both sexes weighing 120-200 g. The hypokinesia model was created by placing the animals in special chambers that restrict motor activity. The control animals had free motion.

The content of acetylcholine was determined in the musculus rectus abdominis of the frog [12] and was expressed in micrograms per 1 g of moist tissue. In order to increase the sensitivity of the preparation acetone was used [13]. The activity of choline acetyltransferase was determined [11] and expressed in micrograms of acetylcholine synthesized by the atria or ventricles in the space of one hour at 37°C in conversion for 1 g of tissue dried with acetone. The Kaplan-Lipmann enzyme of acetylation was extracted from the liver of pigeons [10]. The activity of cholinesterase was analyzed manometrically on the Varburg apparatus. The heart was washed in a 0.9% solution of NaCl, the ventricles were separated from the atria, dried with filter paper and pulverized in a mortar with the addition of 25 mm of $NaHCO_3$

solution (6 ml for the atria, 10 ml for the ventricles). They were extracted for one hour. The reaction mixture consisted of 1.5 ml of extract and 0.5 ml of substrate dissolved in 25 mM of $NaHCO_3$ solution. Acetyl-β-methylcholine /14 (MeC) was used as the substrate for acetylcholinesterase, and butyrylcholine (BuC) for pseudocholinesterase (final concentrations 2.2 mM). The activity of the enzymes was expressed in milligrams of substrate split by the extract in the space of one hour at 38°C in conversion for one gram of moist tissue.

The sensitivity of the heart to exogenous acetylcholine was studied by introducing the substance into the femoral vein in a dose of 10 μg per 100 g of body weight. The degree of bradycardia was taken into consideration, as well as the duration of the negative-chronotropic effect. The EKG was recorded on an ink-writing oscillograph. The right vagus nerve was stimulated by the ESL-2 electrical stimulator (frequency 50 Hz, duration of impulse 5 ms), at first for 5 s, and then, after restoration of the initial rhythm, repeatedly for one minute. The degree of slowing down of the cardiac contraction was computed.

Results and Discussion

The generalized data on the content of acetylcholine, activity of choline-acetyltransferase and cholinesterase in the heart in the space of 30-day hypokinesia are presented in table 1.

The content of acetylcholine in the heart of control animals fluctuated in fairly broad limits, whereupon the atria was six times richer in this mediator than the ventricles. In hypokinesia the content of acetylcholine

in the atria was gradually increased, starting from the 8th day, and by the 30th day was 1.5 times greater than the control amounts. The level of acetylcholine in the ventricles displayed a relative stability and for 30 days practically was not changed. At the end of the observation the correlation between the concentrations of acetylcholine in the atria and the ventricles shifted in favor of the atria.

TABLE 1. CONTENT OF ACETYLCHOLINE, ACTIVITY OF CHOLINACETYLTRANSFERASE AND CHOLINESTERASE[1] IN HEART NORMALLY AND DURING HYPOKINESIA (M±m)

Index	Control	Day of Hypokinesia			
		4-й	8-й	16-й	30-й
Content of acetylcholine:					
Atria	3,72±0,27 (40)	3,04±0,25 (10)	4,71±0,71 (10)	4,51±0,75 (10)	5,40±0,39*(10)
Ventricles	0,63±0,04 (40)	0,52±0,08 (10)	0,78±0,10 (10)	0,62±0,07 (10)	0,67±0,07 (10)
Activity of cholinacetyltransferase:					
Atria	794±60,8 (12)	726±35,2 (10)	688±79,8 (9)	630±43,5*(11)	473±61,2*(10)
Ventricles	647±63,0 (11)	609±52,1 (12)	583±60,9 (11)	272±32,0*(13)	194±45,5*(13)
Activity of acetylcholinesterase:					
Atria	8,64±0,83 (11)	7,84±0,60 (10)	12,15±0,62*(10)	10,53±0,69 (10)	8,51±0,30 (11)
Ventricles	3,07±0,21 (12)	3,25±0,24 (10)	5,27±0,77*(10)	4,53±0,49*(10)	4,27±0,50*(11)
Actvity of pseudocholinesterase:					
Atria	44,75±1,55 (11)	51,44±1,92*(10)	50,83±1,77*(10)	45,56±2,48 (10)	51,60±2,25*(11)
Ventricles	15,61±1,66 (12)	18,41±0,76 (11)	24,57±1,81*(10)	26,94±1,74*(12)	33,68±2,06*(11)

[1]Units of measurement given in section "technique."

Note. The asterisk designates amounts that reliably differ from the controls. In the parentheses number of experiments.

The activity of cholinacetyltransferase was also higher in the atria, but the differences were less pronounced than in the distribution of acetylcholine. During the period of hypokinesia the activity of the enzyme was

gradually reduced in both sections of the heart, which became especially noticeable from the 16th day. In the atria this decrease was less significant than in the ventricles.

The activity of acetyl-and pseudocholinesterase of the atria in the control rats was roughly 2.5 times greater than that in the ventricles. The breakdown ability of one gram of the atria in relation to MeC was 5.01-14.45 mg of substrate, and in relation to BuC--36.66-52.16 mg in 30 minutes. One gram of tissue of the ventricles in the same time broke down respectively 1.99-4.10 mg of MeC and 6.46-27.71 BuC. The activity of acetylcholinesterase was reliably increased in both sections of the heart by the 8th day of hypokinesia, then a decrease started that ended in the atria with complete normalization by the end of the observation. In the ventricles the activity of this enzyme was also reduced after the 8th day, but by the 30th day had not reached the control amounts. The activity of pseudocholinesterase in the atria was increased already on the 4th day of hypokinesia, i.e., at an earlier stage than acetylcholinesterase. By the 16th day the activity of the enzyme had been normalized, but by the 30th a repeated increase was noted. In the ventricles the activity of pseudocholinesterase reliably rose only on the 8th day, i.e., later than in the atria. Then its activity continued to steadily increase and by the 30th day was doubled as compared to the control.

The findings indicate that for hypokinesia an imbalance is characteristic in physiological correlations between individual links in the system cholin-acetyltransferase-acetylcholinesterase. Maintenance of the concentration of acetylcholine on a normal level in the cardiac ventricle and even an increase

TABLE 2. SENSITIVITY OF THE HEART TO EXOGENOUS ACETYLCHOLINE AND TO STIMULATION OF THE VAGUS NERVE IN DIFFERENT PERIODS OF HYPOKINESIA (M±m)

Conditions of Experiments (in parentheses number of animals)	Introduction of Acetylcholine		Stimulation of Vagus Nerve					
			For 5 Minutes		For 1 Minute (Degree of Delay in Rhythm, % of Original			
	Degree of Delay in Rhythm, % of Original	Duration of Bradycardia s	Degree of Delay in Rhythm, % of Original	Duration of Bradycardia s	Immediately After Stimulation	In 5 s	In 30 s	In 1 min
Control (12)	29,9±4,17	3,6±0,35	11,7±2,77	7,0±0,24	13,7±2,39	11,7±1,89	23,5±3,03	39,2±4,87
Hypokinesia:								
4 days (12)	22,7±2,30	4,4±0,23	7,7±2,09	8,6±0,48	10,0±1,79	12,4±3,57	18,3±1,84	25,0±2,77
8 days (12)	20,9±2,30	4,1±0,37	8,0±2,09	8,7±0,35	9,7±1,41	6,1±2,07	15,7±2,00	21,2±1,58
16 days (12)	18,8±2,05	5,3±0,48	5,0±1,70	8,3±0,24	10,7±1,05	5,8±1,48	14,8±1,82	20,8±1,95
30 days (12)	19,0±4,19	4,7±0,52	9,4±2,07	6,3±0,17	12,3±1,30	6,9±1,45	15,0±1,26	19,1±1,14

in it in the atria on the 30th day of hypokinesia indicates considerable adaptation potentialities of the cholinergic regulation of the cardiovascular system. On the other hand it is necessary to assume that guarantee of fairly high concentrations of acetylcholine in the heart is linked not only to the activity of the synthesizing and splitting enzymes, but also to other factors--energy supply, level of initial products, and electrolyte composition of the medium.

Data on the reactions of the heart to exogenous acetylcholine and to /16
stimulation of the vagus nerve are presented in table 2. They indicate the increase in the sensitivity of the heart to exogenous acetylcholine which is manifest in an increase in the degree and duration of bradycardia. Experiments with stimulation of the vagus nerve also indicate the increase in sensitivity of the heart to the cholinergic effects on the 4th-16th day. However by the 30th day a complete restoration of reactions to stimulation of the vagus nerve is noted which was not observed with the introduction of acetylcholine from the outside.

REFERENCES

1. Boyer, V. A. in Meditsinskiye problemy fizicheskoy kul'tury ["Medical Problems of Physical Culture"], Kiev, No 1, 1971, p 10-14.

2. Boyer, V. A. Vliyaniye gipokinezii na funktsii i kholinergicheskuyu regulyatsiyu serdtsa zhivotnykh y razlichnyye vozrastnyye periody ["Effect of Hypokinesia on Function and Cholinergic Regulation of Heart of Animals in Different Age Periods"], author's abstract of candidate dissertation, Chernovtsy, 1972.

3. Kratkiy spravochnik po kosmicheskoy biologii i meditsine ["Concise Reference on Space Biology and Medicine"], edited by A. I. Burnazyan. Moscow, 1972.

4. Davydov, O. V. Voyen.-med. zh., No 3 (1974), p 59.

5. Korneyeva, V. V.; and Ushakov, A. S. Fiziologicheskiye problemy detrenirovannosti ["Physiological Problems of Detraining"], Moscow, 1970, pp 127-133.

6. Panferova, N. Ye. Gipodinamiya i serdechno-sosudistaya sistema ["Hypodynamia and Cardiovascular System"], Moscow, 1977.

7. Simonenko, V. V. in Problemy kosmicheskoy biologii ["Problems of Space Biology"], Moscow, vol 13, 1969, pp 42-49.

8. Ushakov, A. S.; Korneyeva, N. V.; and Vitollo, A. S. in Fiziologicheskiye i klinicheskiye problemy adaptatsii cheloveka i zhivotnogo k gipertermii, gipoksii i gipodinamii ["Physiological and Clinical Problems of Adaptation of Man and Animals to Hyperthermia, Hypoxia and Hypodynamia"], Moscow, 1975, pp 147-149.

9. Fedorov, B. M. Emotsii i serdechnaya deyatel'nost' ["Emotions and Cardiac Activity"], Moscow, 1977.

10. Novelli, G. D. Meth. Biochem. Anal., vol 2, 1958, p 189.

11. Tucek, S. Physiol. Bohemoslov., vol 13, 1964, pp 39-47.

12. Vlk, J., Tucek, S., Ibid., vol 10, 1961, pp 65-71.

13. Zeleny, A., Kozak, J., Nature, vol 181, 1958, pp 1340-1341.